

### **Remarks**

Claims 1-3 and 6-15 were pending prior to this Response, with claims 8-12, 14 and 15 having been withdrawn from further consideration pursuant to 37 C.F.R. § 1.142(b). By the present communication, no claims have been added, claim 1 has been amended to define Applicants' invention with greater particularity, and claims 6 and 8-15 have been canceled without prejudice. Applicants respectfully request entry of the amendments set forth in this response under 37 CFR §1.116. The amendments do not raise any issues of new matter and the amended claims do not present new issues requiring further consideration or search. Support for amended claim 1 may be found, among others, at page 14, lines 27-29; and at page 16, lines 7-8 of the specification. Accordingly, claims 1-3 and 7 are currently pending in this application.

### **Information Disclosure Statement**

The Examiner alleges that the Information Disclosure Statement filed on January 29, 2002 fails to comply with 37 CFR 1.98(a)(1) because a copy of the attached PTO-1449 is not found in the file. Attached herewith as Exhibit A are copies of the Information Disclosure Statement as filed by Applicants with stamped return receipt postcard indicating receipt of PTO-1449 by the USPTO on January 29, 2002. Accordingly, entry and consideration of PTO-1449 as entered on January 29, 2002 is respectfully, requested.

### **Claim Objections**

Applicants respectfully traverse the objection to claims 6 and 13 as allegedly being of improper dependent form for failing to further limit the subject matter of the previous claim. Applicants have canceled claims 6 and 13, rendering the objection moot. Accordingly, Applicants respectfully request withdrawal of the objection.

### **Rejection under 35 U.S.C. § 112, Second Paragraph**

Applicants respectfully traverse the rejection of claims 1-3, 6-7 and 13 as allegedly being

indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner alleges that it is unclear if claim 1 requires that the natural or attenuated toxin have a formalin molecule bound to a lysine residue of the toxin. Applicants have amended claim 1 to clarify that the adjuvant of claim 1 comprises an attenuated toxin that retains serine, glutamic acid, and lysine residues at the original positions in the corresponding natural toxin, but one or more lysine residues in the attenuated toxin is bound to a formalin molecule. Accordingly, reconsideration and withdrawal of the rejection of claims under 35 U.S.C. § 112, second paragraph are respectfully requested.

**Rejection under 35 U.S.C. § 102(b)**

Applicants respectfully traverse the rejection of claims 1, 3, 6, 7 and 13 as allegedly anticipated by Esposito et al (hereinafter "Esposito"). Applicants' amended claims to an adjuvant distinguish over the disclosures of Esposito by requiring an attenuated toxin (i) having a residual toxic activity of less than one-two thousandth ( $<1/2000$ ) that of the natural toxin corresponding thereto and (ii) having an activity of enhancing production of an antibody specific to an antigen other than the attenuated toxin, wherein said attenuated toxin retains serine residues, glutamic acid residues, and lysine residues of the natural toxin in its amino acid sequence, except that a formalin molecule is bound to one or more lysine residues of the toxin, and wherein said toxin is selected from the group consisting of cholera toxin, pertussis toxin, heat-labile toxin of pathogenic *E. coli*, Staphylococcus  $\alpha$  toxin and  $\beta$  toxin, and thermostable hemolytic toxin of *Vibrio parahaemolyticus*.

Esposito discloses that an attenuated cholera toxin can be obtained via chemical treatment with formalin, and state that crude cholera toxin that is converted to toxoid by treatment with 0.2% formalin at 35°C for 4 days proved to be three to five times more antigenic in guinea pigs and rabbits than the parent toxin on an equivalent dose basis. Esposito neither teaches nor suggests the adjuvant activity of the attenuated cholera toxin as a specific *antigen*, and therefore does not have the activity of *enhancing* production of an antigen-specific antibody.

Anticipation under 35 U.S.C. § 102(b) requires that the reference recite each and every

In re Application of:  
Aizawa et al.  
Serial No.: 09/830,019  
Filed: September 21, 2001  
Page 5

PATENT  
Attorney Docket No. SHIM1120

element of the claims in a single document. Since Esposito et al. fails to disclose each and every element of the invention adjuvant, as defined by amended claim 1, Applicants respectfully submit that the Examiner has failed to establish anticipation under 35 U.S.C. § 102 (b) over Esposito et al. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

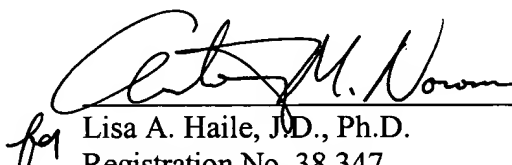
### **Conclusion**

In summary, for the reasons set forth herein, Applicants maintain that claims 1-3 and 7 clearly and patentably define the invention and respectfully request that the Examiner withdraw all rejections and pass the application to allowance. If the Examiner would like to discuss any of the issues raised in the Office Action, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

The Commissioner is hereby authorized to charge any additional fee, or credit any overpayments, to Deposit Account No. 07-1896.

Respectfully submitted,

Date: June 29, 2005

  
for Lisa A. Haile, J.D., Ph.D. *Reg. No. 45,517*  
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DLA PIPER RUDNICK GRAY CARY US LLP  
4365 Executive Drive, Suite 1100  
San Diego, California 92121-2133  
USPTO Customer No. 28213

Enclosure: Exhibit A

**PATENT ATTORNEY DOCKET NO.: SHIM1120**

The Patent and Trademark Office date stamp sets forth the receipt date of:

**Applicant or Patentee:** Aizawa et al. **Filed:** April 19, 2001

**Serial No.:** 09/830,019

**Title:** VACCINE PREPARATIONS CONTAINING ATTENUATED TOXIN

☒ Transmittal Letter (2 pgs)

☒ Information Disclosure Statement (2 pgs.)

☒ Form PTO-1449 (1 pg.)

☒ Number of Prior Art References: 6

Other Return Receipt postcard  
Atty/Sec Initials: LAH/jjb

Client Name: 2102595-3

Date Mailed: 01/14/02

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**PATENT DOCKETING**  
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Aizawa et al. Art Unit: Unassigned  
Application No.: 09/830,019 Examiner: Unassigned  
IA Filing Date: October 20, 1999  
Title: VACCINE PREPARATIONS CONTAINING ATTENUATED TOXIN

Commissioner for Patents  
Washington, D.C. 20231

TRANSMITTAL SHEET

Transmitted herewith for the above-identified application please find:

1. Information Disclosure Statement (2 pages);
2. Form PTO-1449 (1 page);
3. Six (6) References;
4. Return postcard.

CERTIFICATION UNDER 37 CFR §1.8

I hereby certify that the documents referred to as enclosed herein are being deposited with the United States Postal Service as first class mail on January 14, 2002, in an envelope addressed to:  
Commissioner for Patents, Washington, D.C. 20231

Jason Berry

In re Application of:  
Aizawa et al.  
Application No.: 09/830,019  
IA Filing Date: October 20, 1999  
Page 2

PATENT  
Attorney Docket No.: SHIM1120

This Information Disclosure Statement is being filed prior to the receipt of a First Office Action on the merits. Therefore, no fee is deemed necessary in connection with this filing. However, if any fee is required, authorization is hereby given to charge the amount of any such fee, or credit any overpayment, to Deposit Account No. 50-1355.

Respectfully submitted,

Date: \_\_\_\_\_

1/14/02



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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Aizawa et al.	Art Unit:	Unassigned
Application No.:	09/830,019	Examiner:	Unassigned
IA Filing Date:	October 20, 1999		
Title:	VACCINE PREPARATIONS CONTAINING ATTENUATED TOXIN		

Commissioner for Patents  
Washington, D.C. 20231

INFORMATION DISCLOSURE STATEMENT

Sir:

In accordance with 37 C.F.R. § 1.97(2)(i), enclosed are references relating to the above-identified application. For the convenience of the Examiner, these references are listed on the attached Form PTO-1449 and copies are enclosed herewith.

It is respectfully requested that these references be made of written record in this application.

CERTIFICATION UNDER 37 CFR §1.8

I hereby certify that the documents referred to as enclosed herein are being deposited with the United States Postal Service as first class mail on January 14, 2002, in an envelope addressed to:  
Commissioner for Patents, Washington, D.C. 20231

*John Berry*

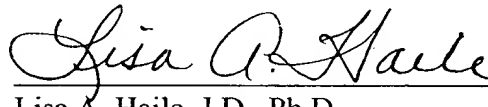
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Page 2

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Respectfully submitted,

Date: 1/14/02



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<b>FORM PTO-1449</b> U.S. Department of Commerce Patent and Trademark Office	<b>Docket No. (Optional)</b> SHIM1120	<b>Serial No.:</b> 09/830,019
	<b>Applicant(s):</b> Aizawa et al.	
<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>	<b>IA Filing Date:</b> October 20, 1999	<b>Group Art Unit:</b> To be assigned

### U.S. PATENT DOCUMENTS

EXAM. INITIALS		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB-CLASS	FILING DATE

### FOREIGN PATENT DOCUMENTS

EXAM. INITIALS		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION (YES/NO)
	AA	WO 95/17211	06/29/1995	PCT			
	AB	WO 95/34323	12/21/1995	PCT			
	AC	WO 98/18928	05/07/1998	PCT			
	AD	WO 98/42375	10/01/1998	PCT			

### OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages)

	AE	Liang, Xiaoping et al., "Cholera Toxin as a Mucosal Adjuvant Glutaraldehyde Treatment Adjuvanticity from Toxicity," <i>The Journal of Immunology</i> , Vol. 143(2), 1989, pgs. 484-490.
	AF	Ryan, Mark et al., "Pertussis Toxin Potentiates T <sub>h</sub> 1 and T <sub>h</sub> 2 Responses to Co-injected Antigen: Adjuvant Action is Associated with Enhanced Regulatory Cytokine Production and Expression of the Co-stimulatory Molecules B7-1, B7-2 and CD28," <i>International Immunology</i> , Vol. 10, No. 4, 1998, pgs. 651-662.

EXAMINER	DATE CONSIDERED
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EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.